



Article Entropy Generation and Control: Criteria to Calculate Flow Optimization in Biological Systems

José Eduardo Pereira Wilken Bicudo ¹, Pedro Góes Nogueira-de-Sá² and José Guilherme Chaui-Berlinck ^{2,*}

- School of Earth, Atmospheric and Life Sciences, University of Wollongong, Wollongong 2522, Australia; jebicudo@ib.usp.br
- ² Departamento de Fisiologia, Instituto de Biociências, Universidade de São Paulo, São Paulo 05508-090, SP, Brazil; pedro.nogueira.sa@usp.br
- * Correspondence: jgcb@usp.br

Abstract: Living beings are composite thermodynamic systems in non-equilibrium conditions. Within this context, there are a number of thermodynamic potential differences (forces) between them and the surroundings, as well as internally. These forces lead to flows, which, ultimately, are essential to life itself, but, at the same time, are associated with entropy generation, i.e., a loss of useful work. The maintenance of homeostatic conditions, the tenet of physiology, demands the regulation of these flows by control of variables. However, due to the very nature of these systems, the regulation of flows and control of variables become entangled in closed loops. Here, we show how to combine entropy generation with respect to a process, and control of parameters (in such a process) in order to create a criterium of optimal ways to regulate changes in flows, the coefficient of flow-entropy $(C^{J\sigma})$. We demonstrate the restricted possibility to obtain an increase in flow along with a decrease in entropy generation, and the more general situation of increases in flow along with increases in entropy generation of the process. In this scenario, the $C^{J\sigma}$ aims to identify the best way to combine the gain in flow and the associated loss of useful work. As an example, we analyze the impact of vaccination effort in the spreading of a contagious disease in a population, showing that the higher the vaccination effort the higher the control over the spreading and the lower the loss of useful work by the society.

Keywords: entropy generation; control; elasticities; flow; optimality; physiology; biology; thermodynamics

1. Introduction

Life is maintained by flows, and it evolves by means of selective pressures. Thus, the flows, which encompass a wide range of biological phenomena from enzymatic reactions to population dynamics, are under the natural selection paradigm as well. Then, can we use a given flow as a criterion of selection? If so, which would such a criterion be?

Homeostasis, the maintenance of the organic internal media under adequate conditions [1], is the basic principle in physiology, and it is akin to cybernetics comprising information and control [2,3]. Therefore, at first glance, one would consider the control of a given flow as a criterion of its relevance and thus how it was eventually shaped by natural selection. In the next two paragraphs, we shall examine why this cannot be an adequate criterion.

Flows are related to unbalanced forces and conductance properties of a system. For instance, the flow in the circulatory system can be written as:

$$J_{co} = X_P \cdot G_{per} \tag{1}$$

where J_{co} is the cardiac output (the flow), X_P is the pressure difference between the arterial and the venous trees (the unbalanced force) and G_{per} is the peripheral vascular conduc-



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Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). tance (the inverse of the peripheral resistance). From the control engineering standpoint, the cardiac output is a regulated variable while the pressure difference and the conductance are controlled variables [4,5]. In this sense, pressure and conductance are directly under a certain policy rule to regulate the flow, which is not directly accessed by the controlling system.

However, both pressure and conductance are, at a second level, controlled variables on their own, since they are regulated by a series of underlying mechanisms. For instance, among other variables, arteriolar wall muscle tone regulates peripheral conductance and myocardial contraction force regulates arterial pressure (e.g., [6–8]). The control of these muscles occurs at a cellular level, and then, they become controlled variables at a third level, and these nested levels of regulation/control will proceed to a number of steps. Because they operate basically in closed control loops among the levels, trying to identify or isolate the "fundamental controlling variables" becomes a search for the holy grail: from one perspective, a given variable is regulated while it is controlled from another (Figure 1). Therefore, the search for adaptation in flows is of a different kind than the search for adaptation in morphological traits.



Figure 1. A general picture of levels of biological regulation/control. While the reductionist view would consider the upward processes at the left-hand side of the scheme as mandatory in controlling flows, the downward closed loops shown on the right-hand side create an entanglement between levels of biological organization that somehow precludes a simple cut-off of what is a controlled and what is a regulated variable (see, for instance, [9,10]). This is valid within the organism and among organisms as well since the biotic and abiotic environments would also dictate access to resources.

2. Flows and Optimization

We can identify that this search for optimization criteria in flows has three strands: the phylogenetic, the ontogenetic, and the adjustment (phenotypic plasticity) levels. Despite being closely related, these levels might not be imbricated in each other in a variety of circumstances. From these strands, the most prominent is the phylogenetic search for optimization since this is the level where natural selection emerges more clearly (e.g., [11,12]). This reasoning, however, might be accompanied by a pitfall. Since adaptation is a continuous process, the search relies on finding local minima or maxima and not global optima [13]. This means that different species might seem to behave differently under the same criterion.

Then, what would be an adequate non ad hoc criterion for the optimization of a given biological flow? From the preceding discussion, one would suppose that the process generating the flow is underway to a local maximum or minimum, but it is close enough to the local extremum to be clearly identified. Once again, an inference must be made: the organism passes most of its time under a certain value of the flow in focus; otherwise, it makes no sense in considering the value of the flow as a selected variable.

From the last paragraph, we can see some problems that hinder the search for optimality criteria in biological flows. Because the extremum is local and one cannot say whether it is already attained or not, and because time must be taken into account, one risks becoming tautological: it is optimum because it is what one observes.

On the other hand, a predetermined criterion might partially circumvent this tautological pitfall. Historically, this predetermined criterion comes from the energetic bias. Power input to and/or power output from a given process (flow) are employed to address the quest for optimization. The success of such an approach is so widespread that it would be impossible to summarize its results in this review (see, for instance, [14,15]).

3. Thermodynamic Criteria for Optimization

The energetic bias has a crucial aspect. Arising from thermodynamic grounds, it offers a lower risk of a tautological criterion for extrema, and it also offers limitations to extrema as well. However, as one might suspect, pitfalls are lurking every now and then.

Let us consider hibernation in mammals. Many hibernators spend months under the torpid condition, and depending on the species and the surrounding environment, this may last for most of the year (e.g., [16,17]). Therefore, combining extremely low metabolic values with the "time under a condition" criterion, the torpid metabolic rate would be the flow under selection and not basal or resting metabolic rate as we would expect and consider for other species [15,18–22]. This example illustrates that to interpret the selection acting on biological flows is potentially deceitful.

Evidently, reproductive success is paramount to evolution, and, from this perspective, the measure of its selective advantage is the prevalence of a given genome in the population (e.g., [23,24]). In this sense, the torpid condition of the above example certainly contributes to the reproductive success of the species, but reproduction per se does not occur in the torpid condition. And by the genomic bias, all optimizations of physiological processes become tautological: they are what is measured in the population that has been selected.

Given this very intricate picture, can we find another way to approach some features of physiological and biological flows in general that might help us understand the evolutionary pressure or its consequences over a given flow?

4. The Present Approach to Optimization

We propose that instead of looking directly at a given flow from any given bias, one asks whether the regulation of this flow follows an optimal path. In other words, when a given flow $J_i(A)$ of a process "i" under condition "A" is lead to $J_i(B)$ under condition "B", does this follows an optimal path? Note that we are not asking whether $J_i(A)$ or $J_i(B)$, or both, are extrema. We are concerned about how optimal the transition between conditions is.

Then, how do we establish what is an optimum path? Certainly, thermodynamic criteria are the best choices for a series of reasons. Firstly, they are prone to be quantified and we unambiguously know what is meant by efficiency in this frame. Secondly, one way or the other, they rule the time evolution of non-biological systems and, thus, living beings inherit such an inescapable realm. Thirdly, classical thermodynamics begins with clear definitions of what is the system under study and, consequently, what are the surroundings. Finally, flows are generated by thermodynamic potentials and, thus, it becomes quite natural and pervasive to consider thermodynamic criteria as the best choice to study selection in physiological flows.

Let us consider flows in general. In conditions near equilibrium, a flow J is the product of an unbalanced force or potential difference X by a conductance G [25,26]. As for the equation for cardiac output presented in the beginning, we have:

$$J = X \cdot G \tag{2}$$

An essential feature of a thermodynamic flow is that they tend to extinguish unbalanced forces and, therefore, they tend to extinguish themselves. In other words, after a certain characteristic time, which depends on the conductance G, $X \rightarrow 0$ and $J \rightarrow 0$. Thus, if nothing else occurs, the system tends to equilibrium. Likewise, in order to keep a flow at a given rate, unbalanced forces must be sustained.

Now, if the system is left to evolve without any other agent at play, the extinction of the unbalanced force X equates to the loss of capacity to perform useful work by the system, i.e., a decrease in its free energy and an increase in its entropy [27–29]. For instance, let us briefly examine the loss of useful work in the isothermal diffusive process. Variation in Gibbs free energy, dG^{ibbs} , is given as:

$$dG^{ibbs} = VdP - SdT \tag{3}$$

where V is volume, P is pressure, S is entropy and T is temperature. Given the isothermal condition, dT = 0, and rearranging the ideal gas equation, we have:

$$VdP = \frac{n}{C}RTdC$$
(4)

where n is the number of mols, C is the concentration and R is the universal gas constant. Thus, the loss in useful work due to the diffusive flow equating the initial concentration in the system to the concentration in the infinite pool of the surroundings is:

$$\Delta G^{\text{ibbs}} = W_{\text{loss}} = nRTln\left(\frac{C_{\text{surr}}}{C_{\text{initial}}}\right)$$
(5)

where, for the sake of simplicity and without any loss of generality, we consider $C_{\text{final}} < C_{\text{initial}}$. This ΔG^{ibbs} equates, then, with the entropy increase as $T\Delta S = -\Delta G^{\text{ibbs}}$. On the other hand, if the initial concentration in the system is kept constant despite the outflow of molecules, then the time derivative of the lost work is the most useful power in the system:

$$\dot{W}_{loss} = \frac{dn}{dt} RT ln\left(\frac{C_2}{C_1}\right)$$
(6)

where C_2 and C_1 are fixed values. Note that $\frac{dn}{dt}$ is the flow of molecules and the rest of the equation to its right side is the chemical potential. From this example, we now proceed to generalizations.

4.1. Entropy Generation

An important branch of contemporary thermodynamics is exergetic analysis, which combines the 1st and the 2nd Laws of thermodynamics into a single approach [28–30]. In this approach, it is considered the maximum useful work that can be extracted from a system when it is lead, reversibly, to the ground state, i.e., it attains mechanical, thermal, and chemical equilibrium with the surroundings through reversible paths. If the system experiences irreversible processes, entropy generation by these processes decreases the exergetic efficiency by destroying exergy, which corresponds to a degradation of the surroundings. Considering that in living beings the basic source of energy input is a decrease in Gibbs' free energy from combustibles (basically glucose and similar sugars), there is a high degree of coincidence between the energetic and the exergetic analyses (Silvio de Oliveira Junior and Carlos Eduardo Mady personal communication). In facing this wide picture, we shall focus in entropy generation.

Near equilibrium entropy generation σ is given by [25,31]:

$$\sigma = \frac{J \cdot X}{T} = \frac{X^2 \cdot G}{T} \tag{7}$$

For the sake of notation, we are omitting the subscript "i" referring to each process in the system. Also, for simplicity, we shall not be concerned with the coupling between potentials, as in the electrochemical potential. As one can see, the entropy generation is a direct measure of how much the system degrades its surroundings in order to keep a given flow that sustains life. Or, alternatively, σ is related to the non-efficiency of a system in keeping a given flow. Therefore, even though less comprehensive than the exergetic approach, this is as well an appropriate thermodynamic criterion for analyses (see, also, [32,33]).

4.2. Coefficients of Control

As we stated earlier, both X and G can be studied as controlled variables. Consider a set of parameters $\mathbf{K} = \{k_1, k_2 \dots k_n\}$ in such a way that, for a given process "i":

$$X = f_X(\mathbf{K}) \tag{8a}$$

$$G = f_G(\mathbf{K}) \tag{8b}$$

$$\Gamma = f_{\rm T}(\mathbf{K}) \tag{8c}$$

Consider a certain parameter $k_a \in \mathbf{K}$. Then, flow regulation by the parameter k_a implies in:

$$\frac{\partial J}{\partial k_a} = \frac{\partial X}{\partial k_a} \cdot G + \frac{\partial G}{\partial k_a} \cdot X \tag{9}$$

and the relative variation (i.e., elasticity) of flow is:

$$\frac{\frac{\partial J}{J}}{\frac{\partial k_a}{k_a}} = \frac{\partial J}{\partial k_a} \cdot \frac{k_a}{J} = \left(\frac{\partial X}{\partial k_a} \cdot G + \frac{\partial G}{\partial k_a} \cdot X\right) \cdot \frac{k_a}{X \cdot G} = \frac{\partial X}{\partial k_a} \cdot \frac{k_a}{X} + \frac{\partial G}{\partial k_a} \cdot \frac{k_a}{G}$$
(10)

For historical reasons, the elasticity $\frac{\partial J}{\partial k_a} \cdot \frac{k_a}{J}$ is named "flux control coefficient" (by the parameter k_a) [34–38]:

$$C_{k_a}^{J} = \frac{\partial J}{\partial k_a} \cdot \frac{k_a}{J} = C_{k_a}^{X} + C_{k_a}^{G}$$
(11)

Applying the elasticity concept to the entropy generation (Equation (7)), one obtains (we omit the intermediate algebra):

$$C_{k_{a}}^{\sigma} = 2 \cdot C_{k_{a}}^{\chi} + C_{k_{a}}^{G} - C_{k_{a}}^{T}$$
(12)

Then, combining Equations (11) and (12), we obtain a new coefficient of elasticity associating relative changes in flow to relative changes in entropy generation when there is a variation in the parameter k_a :

$$\frac{C_{k_a}^{\sigma}}{C_{k_a}^{J}} = C_{k_a}^{J\sigma} = \frac{2 \cdot C_{k_a}^{\chi} + C_{k_a}^{G} - C_{k_a}^{T}}{C_{k_a}^{\chi} + C_{k_a}^{G}}$$
(13)

And we name this new quantity the flow-entropy coefficient. It must be understood that the flow-entropy coefficient is a value related to changes in a given parameter k_a of the system and that it is in respect to a certain process (or flow). Taking for granted that these are implied in the notation, we simplify the flow-entropy coefficient to:

$$C^{J\sigma} = C^{J\sigma}_{k_2} \tag{14}$$

Now, there is a term whose meaning must be clarified before we proceed. As we stated earlier, the system and, consequently, the surroundings are to be defined at the beginning of the analysis. Therefore, one might consider the surroundings' temperature as the reference, and then, each process "i" contributes with its σ_i in the total entropy generation of the system as a non-reversible heat loss to the surroundings. In a vast number of cases, within the time scale of the changes in a given flow, the surroundings can be taken as an infinite pool and, thus, one can consider $C_{k_a}^T = 0$ for the purposes of the analysis. This $C_{k_a}^T = 0$ will

be assumed in the remaining of the present text, except in the working example at the end. Then, Equation (13) becomes:

$$C^{J\sigma} = \frac{2 \cdot C^X + C^G}{C^X + C^G}$$
(15)

where it is understood that the elasticities are related to some parameter ka.

A last thing must be said before we continue. Elasticities, and therefore control coefficients, are non-dimensional quantities, i.e., they are pure numbers. When computing a given coefficient, it is important to check out if the resulting value is a pure number since these computations might become quite demanding in some cases.

4.3. The Values of $C^{J\sigma}$

For sure, the next question in mind is how Equation (15), i.e., the flow-entropy coefficient $C^{J\sigma}$, can be of any help. The answer to this question is quite clear: The lower the value of $C^{J\sigma}$ the more a flow can be increased relative to the entropy generation of the process. In other words, lower $C^{J\sigma}$ values indicate optimal paths to increase a given flow.

From the preceding paragraph, one would conjecture that to obtain an increase in flow along with a decrease in entropy generation is "the best of both worlds." That is, paths that have $C^{J\sigma} < 0$ are the best choices. Let us examine Equation (9) and ask how a positive change (i.e., an increase) in flow might be brought about. Rewriting Equation (9) as a positive change in flow, we have:

$$dJ = dk_a \left(\frac{\partial X}{\partial k_a} \cdot G + \frac{\partial G}{\partial k_a} \cdot X \right) > 0$$
(16a)

Developing the term between parenthesis:

$$\frac{\partial G}{\partial k_{a}} \cdot \frac{X}{G} > -\frac{\partial X}{\partial k_{a}}$$
(16b)

We now examine a decrease in entropy generation:

$$d\sigma = dk_a \left(\frac{\partial X}{\partial k_a} \cdot 2 \cdot X \cdot G + \frac{\partial G}{\partial k_a} \cdot X^2 \right) < 0$$
(17a)

Developing the term between parenthesis:

$$\frac{\partial X}{\partial k_{a}} \cdot 2 \cdot G + \frac{\partial G}{\partial k_{a}} \cdot X < 0 \tag{17b}$$

Thus:

$$\frac{\partial G}{\partial k_{a}} \cdot \frac{X}{G} < -2 \cdot \frac{\partial X}{\partial k_{a}} \tag{17c}$$

Both X and G are, from our perspective, positive values.

Figure 2 illustrates the conditions for an increase in flow and a decrease in entropy generation (Inequations (16b) and (17c), respectively) due to changes in conductance and force. As can be seen, "the best of both worlds" can be obtained only in narrow band of a few situations where $\frac{\partial X}{\partial k_a} < 0$ and $\frac{\partial G}{\partial k_a} > 0$, and such an existence depends on the actual values of X and G themselves. In other words, it is possible to obtain an increase in flow with a decrease in entropy generation depending on the values of the potential difference and the conductance if the conductance increases while the force decreases. This corresponds to $C^{J\sigma} < 0$.



Figure 2. $\frac{\partial G}{\partial k_a}$ axis as a graphical representation of the solutions of Inequations (16b) and (17c). The solutions pertaining to each inequation are indicated by cross-hatched bands. As it is shown, a simultaneous solution to both inequations is possible only if $\frac{\partial X}{\partial k_a} < 0$ and $\frac{\partial G}{\partial k_a} > 0$. The upper line is for the case $\frac{\partial X}{\partial k_a} > 0$ while the lower line is for the case $\frac{\partial X}{\partial k_a} < 0$.

However, care must be taken when a $C^{J\sigma} < 0$ is found. Notice that "the worst of both worlds" also lurks in the way, since paths in which $C^{J\sigma} < 0$ may indicate that a flow decreases while its entropy generation increases.

The preceding discussion focused on increases of a given flow. What if the flow is to be decreased? Then, we have the specular image of what happens in the increased zone: the higher the $C^{J\sigma}$ value the better the path. This is easy to understand if one considers $C^{J\sigma} = 0$ while dJ < 0. In this situation, the system still deals with the same amount of lost work but has a lower flow rate. Figure 3 summarizes these various situations depicted so far in reference to Equation (15). It is essential to note that for each parameter k_a , the associated $C^{J\sigma}$ value is a single point in the $C^{G}vs.C^{X}$ plane. Alternatively, if $C^{J\sigma}$ turns out as a function of the parameter, then it might assume different values along the changes in k_a . In the final section of the present manuscript, we develop a case study of this last type.

4.4. $C^{J\sigma}$ and Physiological Adjustments

We now turn to another facet of the flow-entropy coefficient. Given the natural selection process, one can conjecture that an organism operating under a given condition has a set of parameters and variables that assume their same respective values whenever the system is in that given condition. This is what makes it possible to compare different individuals and a single individual in different conditions.

Consider the system is at a given condition A and then it transits to another condition B. Both A and B have specified demands (i.e., a given flow) for a given condition; for example, the transition from rest to a moderate level of physical effort, or a temperature change in the surroundings that puts the animal below its thermoneutral zone. Let us assume that the transition is brought about by an increase in parameter k_a , and that the associated coefficient is $C^{J\sigma} = 0.8$. From Figure 3, we can see that this is a fairly good value representing an increase of 0.8 units of entropy production for each unit of increase in flow. Then, the system returns to condition A, decreasing the parameter k_a . Since $C^{J\sigma}$ is the same, the returning path also has a decrease in entropy generation that falls behind the decrease in flow. That is, while in the first transition, the system obtained an advantage in terms of the relationship between the increase in flow and the increase in entropy generation, in the returning transition the system has a disadvantage in the decrease in flow and the decrease in entropy generation.

In other words, one would like to minimize $C^{J\sigma}$ when a given flow is increased, but maximize $C^{J\sigma}$ when a given flow is decreased. However, because $C^{J\sigma}$ is a single function for a parameter k_a , this is not possible. In terms of phylogenetic evolution and ontogenetic development this is not a problem since these are one-way paths that once traveled would be no return. However, for physiological adjustments, the picture is quite different because they are two-way roads.



Figure 3. The C^G vs. C^X plane. The elasticities' coefficients of the conductance G and of the potential X are represented as orthogonal axes. The dashed line corresponds to $C^{G} = -C^{X}$ and the dotted-dashed line corresponds to $C^{G} = -C^{X}$ and the dotted-dashed line corresponds to $C^{G} = -2C^{X}$. These two lines form the boundaries of the "best of both worlds" (bbw) condition of dJ > 0 along with $d\sigma < 0$, and of the "worst of two worlds" (wbw) condition of dJ < 0 along with $d\sigma > 0$. In the outside zones there are two grey areas, one indicating the region with dJ > 0 and $d\sigma > 0$ (dark grey) and the other indicating the region with dJ < 0 and $d\sigma < 0$ (light grey). Both these regions have non-negative $C^{J\sigma}$. However, in the former (dark grey zone), processes that occur in the 2nd quadrant are the most efficient, and processes that occur in the 4th quadrant are the most inefficient, while the opposite occurs in the latter (light grey zone). The 1st and the 3rd quadrants are of intermediate efficiencies in their respective zones. Numbers in parentheses indicate the $C^{J\sigma}$ value over the respective line. For instance, along the C^{X} axis, $C^{J\sigma} = 2$, while along the C^{G} axis, $C^{J\sigma} = 1$. These results come immediately from Equation (15) since walking over one of these axes means to have no changes in the other.

Therefore, it would be expected that optimized physiological adjustments operate transitions in one of two modes. The first is to have $C^{J\sigma} \cong 0$, and then, changes in flow have a low impact on entropy generation one way or the other. Appealing as such a solution might seem, thermodynamic constraints impose severe limits to this option. The second mode is to have hysteresis in the process. For instance, instead of transitions as $A \to B \to A$, one performs $A \to B' \to B \to A' \to A$. While in the final conditions A and B the parameter k_a attains specified values, the intermediate conditions B' and A' comprise changes through other parameters that allow for hysteresis in the cycle. Then, as in the Carnot cycle, the area enclosed by the path represents a net gain in terms of entropy generation in relation to changes in flow.

For the sake of concreteness, let us give an example of hysteresis in flow; in this case, metabolic rate (i.e., oxygen consumption rate). Figure 4 illustrates a schematic representation of the entry to and arousal from a torpor episode by a heterothermic endotherm, as a small mammal in temperate climates. As can be seen in the plot, the arousal is not a mirror image of the entry phase. Then, one could ask whether there is an optimization in entropy generation due to this hysteresis in the process. This is the kind of question that the flow-entropy coefficient $C^{J\sigma}$ tries to answer when dealing with physiological adjustments.



Figure 4. Schematic representation of a torpor bout in a small bird or mammal. Based in [39,40].

5. A Working Example

A more profound analysis of how to employ the flow-entropy coefficient $C^{J\sigma}$ in the phylogenetic domain is presented elsewhere, and there we show the reasons for the observed scaling of blood pressure and volume [32]. Presently, we opted to take a different bias, now in the populational domain, in order to show the broadness of the method analyzing vaccination effort as a control parameter of a contagious disease. The model we use is the common SIR (Susceptible, Infected, Recovered) model plus the vaccinated V state, or the SIRV model (e.g., [41,42]). The present analysis is not intended to bring changes in the current understanding of this model, but to show an alternative way of interpreting the results. The model is given by four differential equations:

$$S = P - a \cdot S \cdot I - v \cdot S - \mu \cdot S$$

$$I = I \cdot (a \cdot S - r - m - \mu)$$

$$V = v \cdot S - \mu \cdot V$$

$$R = r \cdot I - \mu \cdot R$$
(18)

where P is the birth rate of the population, a is the transmissibility or infective constant rate, v is the vaccination constant rate (vaccination effort), μ is the mortality rate for the population in general, r is the recovery from the disease constant rate and m is the mortality constant rate from the disease. Without loss of generality, in this example, the total population is not kept constant.

For the sake of notation, let

$$\mathbf{B} = \mathbf{r} + \mathbf{\mu} + \mathbf{m} \tag{19}$$

The equilibrium point of the system (13) for the endemic case (i.e., $I^* > 0$) is obtained from the second equation of the system, and we have:

$$S^* = \frac{B}{a}$$
(20)

where the superscript "*" is to indicate the value of the state variable at the equilibrium point. From Equation (20), which represents the endemic case, the infected population becomes:

$$I^* = \frac{a \cdot P - B \cdot (v + \mu)}{a \cdot B}$$
(21)

From Equation (21) we can identify a critical value of vaccination effort that eradicates the disease (i.e., $I^* = 0$):

$$v_{\rm crit} = \frac{a \cdot P}{B} - \mu \tag{22}$$

Thus, we examine the model within the range:

$$0 \le v \le v_{crit}$$

Now, we define the generalized flow J as the rate of people becoming infected:

$$\mathbf{J} = \mathbf{a} \cdot \mathbf{S}^* \cdot \mathbf{I}^* \tag{23}$$

where a becomes the generalized conductance G and the product $S^* \cdot I^*$ acts as the generalized force. Equations (20), (21), and (23) become:

$$J = \frac{a \cdot P - B \cdot (v + \mu)}{a} = P - (v + \mu) \cdot S^*$$
(24)

Let us conceive a suitable "temperature" for this system as:

$$\Gamma = H \cdot e^{-z \cdot \Gamma} \tag{25}$$

where H is a normalized number related to per capita income of the given population and z is a constant that relates a decrease in per capita income to the number of infected people I^* . Therefore, the generalized entropy generation is a measure of how the spreading of the infectious disease impacts society, and its equation becomes:

$$\sigma = \frac{J \cdot S^* \cdot I^*}{T} = \frac{J^2}{a \cdot H \cdot e^{-z \cdot I^*}}$$
(26)

To study the effect of vaccination effort in the system, we start by computing the following partial derivatives:

$$\frac{\partial S}{\partial v} = 0$$

$$\frac{\partial I}{\partial v} = -\frac{1}{a}$$

$$\frac{\partial J}{\partial v} = -\frac{B}{a}$$
(27)

Here, we omit the intermediate algebra and present the results straightway:

$$C_{v}^{J} = -\frac{v \cdot B}{a \cdot P - B \cdot (v + \mu)} = -\frac{v \cdot B}{a \cdot J}$$
(28a)

$$C_{v}^{\sigma} = -\frac{v \cdot (2 \cdot B + z \cdot J)}{a \cdot J}$$
(28b)

$$C_{v}^{J\sigma} = -\frac{2 \cdot B + z \cdot J}{B} = 2 + z \cdot \frac{a \cdot P - B \cdot (v + \mu)}{a \cdot B}$$
(28c)

For completeness of the working example, let us check out whether these coefficients are pure numbers. The dimensions involved are [n], number of people, and [t], time. The dimensions of the parameters are presented in Table 1.

Table 1. Dimension of the parameters in system (13).

Parameter	Dimension
Р	[n t ⁻¹]
a	$[n^{-1} t^{-1}]$
В	[t ⁻¹]
v	[t ⁻¹]
Z	[n ⁻¹]

Thus, the flow J has dimension of $[n t^{-1}]$ and the coefficients are non-dimensional quantities, indeed.

 C_v^J is a function of v, negative in this case, indicating that an increase in vaccination effort causes a decrease in infection flow (as expected). Notice that $C_{v=0}^J = 0$ and $C_{v \to v_{crit}}^J \to -\infty$. This is quite an interesting result, indicating that as the vaccination effort increases it gains further control over the disease flow, while for $v \cong 0$ vaccination effort it offers none to little control over the infection flow in the population.

Notice that $C_v^{J\sigma}$ is also a function of v, and thus it is not a single point in the C^G vs. C^X plane (Figure 3): if v = 0, $C_v^{J\sigma} = 2 + z \cdot \frac{a \cdot P - B \cdot \mu}{a \cdot B}$ while if $v = v_{crit}$, $C_v^{J\sigma} = 2$. The positiveness of $C_v^{J\sigma}$ indicates that if the flow increases (due to a reduction in vaccination effort, see above) the generalized entropy generation, i.e., the negative impact over society, increases as well (and vice-versa). Notice also that $C_v^{J\sigma} \ge 2$ for all v, meaning that the vaccination effort causes a disproportional greater change in generalized entropy generation in relation to disease flow. However, in this case, the result is beneficial, since we are interested in decreasing the impact of the disease in society (i.e., we are in the light grey area of Figure 3). Figure 5 shows the plots of $C_v^{J\sigma}$ and of $C_v^{J\sigma}$ as functions of vaccination effort.



Figure 5. $C_v^{J\sigma}$ (red) and C_v^J (blue) versus vaccination effort. See text for detailed discussion.

It is important to note that the approach we exemplify here using $v = k_a$ can be performed for any of the parameters of the model, namely, P, a, μ , r, m, z. As previously mentioned, we do not intend to create a new model of vaccination, nor to analyze the model in terms of its equilibrium points and their respective stability or conditions to eliminate the contagious disease. Instead, our intention is to show an alternative way to interpret the impact of the parameters in the dynamics of the disease.

6. Conclusions

Living beings are systems out of thermodynamic equilibrium, which is implied in the existence of flows both internally and to the surrounding environment. At the same time, homeostasis, the adequate regulation of the internal medium, is what guarantees the continuation of the individual life, and this is implied in the regulation of flows. In the present study, we show that an index called "flow-entropy coefficient" can be used as a measure of optimization in a given process. This coefficient combines the impact of a given parameter in the regulation (change) of a given flow and in the entropy generation associated to such a change in flow.

We have already employed the flow-entropy coefficient to explain the scaling in blood pressure and volume in mammals, and here we show its use to evaluate how vaccination effort in face of a spreading contagious disease impacts the society.

Future studies might include the validation of systems both experimentally and empirically, and the study of homeostatic regulation of specific physiological flows intra and inter specific. Additionally, to examine the use of information entropies in place of the thermodynamic one as a measure of the impact in the system, as, for instance, the Tsallis' S_q entropy to address eventual transitions between super additive and sub additive in the behavior of the system [43], might also prove relevant.

In short, the flow-entropy coefficient is a powerful tool to elucidate relationships between the parameters of a model and concepts such as efficacy, efficiency, optimization, etc.

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